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Πτυχιακή Εργασία

Pancreatogastrostomy versus pancreatojejunostomy after pancreaticoduodenectomy : an up-to-date meta-analysis of randomized controlled trials

Παγκρεατογαστρική έναντι παγκρεατονηστιδικής έπειτα από παγκρεατοδωδεκαδακτυλεκτομή : μετα-ανάλυση προοπτικών τυχαιοποιημένων μελετών

Περιβολιώτης Κωνσταντίνος

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INTRODUCTION

Rationale

Pancreatoduodenectomy (PD) is still the gold standard of treatment for patients with resectable benign and malignant lesions of the head of the pancreas and the periampullary region. Although, PD is considered a safe operative technique, with 30-days mortality rates in specialized, high volume centers currently estimated bellow 3% [1 2], complications , such as postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postpancreatoduodenectomy haemorrhage (POPH), increase the overall morbidity to the rate of 45% , despite the application of enhanced recovery approaches after surgery [3].

Given the fact that the frequency of POPF, the most notorious postpancreatoduodenectomy complication, remains an high as 40% [4] , researchers have focused on factors that may influence this rate, with the pancreatoenteric anastomosis being one of them. The anastomosis between the pancreatic stump and the GI is regarded as prone to leakage , due to exposure of the suture line to pancreatic juice . The two most widely adopted postpancreaticoduodenectomy anastomotic techniques, are the pancreatogastrostomy (PG) and the pancreatojejunostomy (PJ) which combined with anastomotic reinforcing techniques, such as glue and intra-ductal stenting, are designed to provide a sealed and stable pancreatoenteric junction. In current literature, a series of retrospective and prospective studies[5-10] have compared PG and PJ with inconclusive results. Keck et al. [11] ,in a large multicenter randomized controlled trial, reported no difference between the two techniques in terms of clinically significant POPF, which is in contrast with results from previous meta-analyses[12-14], where it was suggested that PG was a safer and more effective method of reconstruction, with lower rates of POPF and other intra-abdominal complications and shorter length of hospital stay (LOS).

Objectives

In light of these conflicting evidence, we conducted a meta-analysis, in order to provide an up-to-date comparison of PG and PJ after PD,for benign or malignant diseases of the head of the pancreas and the periampullary region , in terms of POPF and other postoperative complications .

METHODS

Study protocol

The conduction of this meta-analysis was completed according to the PRISMA [15] guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. The present study was not registrated in any database.

Primary Endpoint

The primary endpoint of this study was the rate of overall postoperative pancreatic fistula. POPF was defined by ISGPF [16] as a drain output of any measurable volume of fluid on or after POD 3 with an amylase content >3 times the serum amylase activity. Classification to grade A, B and C is based on the impact of POPF to the overall clinical course.

Secondary Endpoints

Secondary endpoints included clinically significant POPF (grade B/C), postoperative delayed gastric emptying (DGE) [17], clinically significant DGE (grade B/C), postpancreatectomy haemorrhage (PPH)[18], clinically significant PPH (grade B/C), biliary fistula, intra-abdominal fluid collection, overall morbidity, mortality, reoperation rate, wound infection, intraoperative blood transfusion, operative time and the length of hospital stay (LOS).

Eligibility criteria

Eligible trials were prospective human studies with a RCT design, comparing PG and PJ after PD for benign or malignant diseases of the head of the pancreas and the periampullary region, whose outcome data were reported in English and could be retrieved. Excluded studies included those not written in English, with no outcome of interest, with no comparing group , observational, no randomized and no human studies. Moreover studies reported in the form of editorials, letters, conference abstracts, expert opinion or duplicate studies were excluded.

Literature search

A systematic literature search in electronic databases (MEDLINE and Cochrane Central Register of Controlled Clinical Trials) was performed (search date : 20 July 2016) in order to identify the eligible RCTs.

In order to perform the literature search the following keywords were used :

- MEDLINE: (Pancreaticoduodenectomy OR Pancreatoduodenectomy OR Whipple OR "pancreatoduodenal resection" OR "pancreaticoduodenal resection" OR pancreaticojejunostomy OR pancreatojejunostomy OR "pancreaticoenteric anastomosis" OR "pancreatoenteric anastomosis" OR pancreaticogastrostomy OR pancreatogastrostomy OR "pancreaticogastric anastomosis" OR "pancreatogastric anastomosis"OR "pancreaticojejunal anastomosis" OR "pancreatojejunal anastomosis") AND ("Clinical Trials as Topic" OR "randomized controlled trial" OR "controlled clinical trial" OR randomized OR placebo OR randomly OR trial)
- Cochrane Central Register of Controlled Clinical Trials (Wiley): (Pancreaticoduodenectomy OR Pancreatoduodenectomy OR Whipple OR "pancreatoduodenal resection" OR "pancreaticoduodenal resection" OR pancreaticojejunostomy OR

pancreatojejunostomy OR “pancreaticoenteric anastomosis” OR “pancreatoenteric anastomosis” OR pancreaticogastrostomy OR pancreatogastrostomy OR “pancreaticogastric anastomosis” OR “pancreatogastric anastomosis”OR “pancreaticojejunal anastomosis” OR “pancreatojejunal anastomosis”)

Study selection and Data collection

After duplicate removal, titles and abstracts of the studies were screened according to eligibility criteria. The next step included the full text review of the articles in order to assess that they are consistent with the inclusion criteria.

All electronic database search , study selection, data extraction, and methological assessment of the studies were performed blindly and in duplicate by two independent investigators (PK and SE). Disagreements were resolved by mutual revision and discussion, in order to reach a consensus. In case of not resolving the discrepancies, the opinion of a third investigator (TA) was considered.

From all eligible studies the data extracted included : author’s name, study location and year, RCT type, sample size, the age and gender of the participants, primary outcome, follow up duration, overall morbidity, underlying disease, operation type, rate of PD/pylorus preserving PD (PPPD), anastomotic technique, operative time, postoperative hospital stay, use of intraductal stent , glue and drains , postoperative administration of somatostatin , and information regarding the diameter of pancreatic duct and the texture of pancreas. Only results reported in the article of the studies were extracted.

All studies imported in this meta-analysis were submitted to rigorous quality and methodological evaluation for bias appraisal according to Cochrane’s risk of bias assessing tool[19] . Validity checkpoints included assessment of random sequence allocation, allocation concealment, blinding of participants and personnel and blinding of outcome assessment, incomplete outcome data and selective reporting. Cohen’s k statistic was also calculated.

Statistical Analysis

Data analysis was performed using the Cochrane Collaboration RevMan version 5.3 .Dichotomous variables were reported in the form of Odds Ratio (OR), while for continuous variables Weighted Mean Differences (WMD) were used. Results of the analyses were presented with the corresponding 95% Confidence Interval (95% CI) .

In the case of continuous variables, if the article did not provide the mean and the Standard Deviation (SD), these were calculated from the median and the Interquartile Range (IR), based on the formula by Hojo et al[20]. More specific, if the sample size was >25, then the mean was considered equal to the median. For sample sizes <70 ,SD was regarded as IR/4. If the sample size was >70, then SD was equal to IR/6. For dichotomous variables, the statistical method used was the Mantel-Haenszel (MH) and for continuous variables the Inverse Variance (IV). Both Fixed Effects (FE) and Random Effects (RE) model were calculated. The decision of which model to finally estimate was based on the Cochran Q test. If statistically significant heterogeneity was present (Q test P<0.1) then RE model was applied . Moreover heterogeneity was quantified with the use of I^2. The studies were weighted on the basis of sample size. Statistical significance was considered at the level of P<0.05.

Risk of bias across studies

The funnel plot of the primary outcome was also visually inspected, in order to determine the possible presence of publication bias. An Egger’s test was also performed for the primary outcome.

RESULTS

Study selection

From the literature search, 1240 citations (Figure 1) were retrieved, published up to 20 July 2016. After the removing of 236 duplicate records, the screening of the titles and the abstracts begun. From the 1004 studies submitted to the first phase of the screening, 993 were excluded. More specific, 10 were comments or conference abstracts, 5 did not have a RCT design, 5 did not have a comparison group, 18 were reviews of the current literature, 20 were meta-analysis, 3 articles were not written in English, 23 compared different techniques of PG or PJ instead and 909 were irrelevant to the subject records. In full text review were submitted 11 articles [9 11 21-29]. At this step, 1 trial [9] was rejected due to, a no RCT design. Finally 10 studies [11 21-29] were included in qualitative and quantitative analysis.

Study characteristics

Table 1 summarizes the characteristics of the included studies. The publication date ranges between 1995 up to 2016. Four studies were multi-centered while the other six were single-centered. Fernández-Cruz et al. [24] was the first to adopt the ISGPS definition and classification of POPF. Since then, heterogeneity existed in the definition and diagnosis of POPF. The overall amount of patients included in this meta-analysis is 1629 (Table 2). A total of 826 PGs and 803 PJs were performed . The age of the participants extended from 12 to 87 years . Regarding the gender allocation between the two comparison groups, data are shown in Table 2. El Nakeeb et al. [23] compared the results of PG and an isolated Roux loop pancreatojejunostomy while Fernández-Cruz et al. [24] , respectively compared PJ and PG with gastric partition. In the rest of the studies, PG was considered the intervention and PJ the control. All studies, except Duffas et al.[22] had the rate of POPF as primary outcome. Four studies [21 24 26 29] did not report the duration of follow up. In the other six studies follow up varied from 30 days to 12 months. Regarding the underlying disease, carcinoma of the pancreatic head was the most frequent (Table 3).The PD and PPPD ratio is shown in Table 3. There was a lack of uniformity between the studies regarding the technique of PG and PJ anastomoses. Both PG and PJ could be performed either in a telescoped or a duct-to mucosa manner. Table 4 reports a summary of the studies implementing the use of stents in the pancreatic duct, anastomotic glue reinforcement , and the overall drain use. Postoperative octreotide was administered in 7 studies [21-23 25-28]. All studies reported data regarding the main pancreatic duct diameter . Similarly, only Topal et al. [27] did not provide the allocation of the patients regarding pancreatic texture.

Risk of bias within studies

Figure 2 represents a summary of the included studies quality assessment. More specifically, as shown in Figure 3, all studies included a random sequence generation procedure in their protocol. Allocation concealment was also applied in all studies except one [29]. Only two trials [11 22] reported the blinding of participants and personnel and the blinding of outcome assessment. Only in the study of Grendar et al. [26] incomplete outcome data and possible selective reporting was detected. There was almost perfect agreement between the two investigators (Cohen’s k statistic : 82.3% p<0.001)

Primary Endpoint

- All the included studies (Figure 4) provided comparison between the two anastomotic techniques regarding POPF. In summary, 138 patients from a total of 826 submitted to PG developed POPF, instead of 175 and 803 respectively in the PJ group. Meta-analysis of these data showed a statistically significant (p=0.008) lower ratio of POPF (OR:0.71, 95%CI : 0.55

- 0.91) for the PG group. Since there was no significant heterogeneity between the studies (Q test P:0.27, I^2 :19%(95%CI : 0-59.8%)), a FE model was applied.

Secondary Endpoints

- All ten studies (Figure 6) compared the two anastomotic techniques regarding the clinically significant POPF. More specifically 108 patients from a total of 826 in the PG group developed clinically significant POPF, whereas in the PJ group the same ratio was 144/803. Meta-analysis of these data showed no statistically significant (p=0.09) difference between the two groups regarding clinically significant POPF (OR:0.70, 95%CI : 0.46 – 1.06). Since there was significant heterogeneity between the studies (Q test P:0.04, I^2 :48%(95%CI : 0-75%)), a RE model was applied.
- Eight studies (Figure 7) provided data for DGE. Meta-analysis of the data showed no statistically significant (p=0.75) difference between the two groups regarding DGE (OR:1.08, 95%CI : 0.68 – 1.70). Heterogeneity was significant between the studies (Q test P:0.04, I^2 :53%(95%CI : 0-78.9%)), so a RE model was used.
- Eight studies (Figure 8) provided data for clinically significant DGE. Meta-analysis of the data showed no statistically significant (p=0.93) difference between the two groups regarding clinically significant DGE (OR:0.98, 95%CI : 0.59 – 1.63). Heterogeneity was significant between the studies (Q test P:0.03, I^2 :55%(95%CI : 1.7%-79.8%)), so a random effects model was used.
- Eight studies (Figure 9) provided data for PPH. Meta-analysis of the data showed statistically significant (p=0.02) difference between the two groups regarding POPH (OR:1.52, 95%CI : 1.08 – 2.14) in favor of PJ group . Heterogeneity was not significant between the studies (Q test P:0.85, I^2 :0%(95%CI : 0-80.3%)), so a FE model was used.
- Eight studies (Figure 10) provided data for clinically significant PPH. Meta-analysis of the data showed no statistically significant (p=0.10) difference between the two groups regarding clinically significant POPH (OR:1.35, 95%CI : 0.95 – 1.93). Heterogeneity was not significant between the studies (Q test P:0.96, I^2 :0%(95%CI : 0-75.9%)), so a FE model was used.
- Seven studies (Figure 11) provided data for biliary fistula. Meta-analysis of the data showed no statistically significant (p=0.08) difference between the two groups regarding biliary fistula (OR:0.58 , 95%CI : 0.31 – 1.06). Heterogeneity was not significant between the studies (Q test P:0.14, I^2 :38%(95%CI : 0-73.7%)), so a FE model was used.
- Nine studies (Figure 12) provided data for intra-abdominal fluid collection. Meta-analysis of the data showed no statistically significant (p=0.06) difference between the two groups regarding intra-abdominal fluid collection (OR:0.64, 95%CI : 0.40 – 1.02). Heterogeneity was significant between the studies (Q test P:0.07, I^2 :45%(95%CI : 0-74.6%)), so a RE model was used.
- Eight studies (Figure 13) provided data for morbidity. Meta-analysis of the data showed no statistically significant (p=0.82) difference between the two groups regarding morbidity (OR:0.97, 95%CI : 0.77 – 1.23). Heterogeneity was not significant between the studies (Q test P:0.21, I^2 :28%(95%CI : 0-67.5%)), so a FE model was used.
- Ten studies (Figure 14) provided data for mortality. Meta-analysis of the data showed no statistically significant (p=0.94) difference between the two groups regarding mortality (OR:0.98, 95%CI : 0.60 – 1.61). Heterogeneity was not significant between the studies (Q test P:0.94, I^2 :0%(95%CI : 0-76.8%)), so a FE model was used.
- Eight studies (Figure 15) provided data for reoperation rate. Meta-analysis of the data showed no statistically significant (p=0.33) difference between the two groups regarding reoperation rate (OR:0.84, 95%CI : 0.59 – 1.20). Heterogeneity was not significant between the studies (Q test P:0.79, I^2 :0%(95%CI : 0-83%)), so a FE model was used.
- Four studies (Figure 16) provided data for wound infection. Meta-analysis of the data showed no statistically significant (p=0.77) difference between the two groups regarding wound infection (OR:1.08, 95%CI : 0.66– 1.76). Heterogeneity was not significant between the studies (Q test P:0.86, I^2 :0%(95%CI : 0-90%)), so a FE model was used.
- Six studies (Figure 17) provided data for blood transfusion. Meta-analysis of the data showed no statistically significant (p=0.86) difference between the two groups regarding blood transfusion (OR:1.03, 95%CI : 0.72 – 1.47). Heterogeneity was not significant between the studies (Q test P:0.39, I^2 :5%(95%CI : 0-91.4%)), so a FE model was used.
- Ten studies (Figure 18) provided data for operative time. Meta-analysis of the data showed no statistically significant (p=0.41) difference between the two groups regarding operative time (MWD:-5.73, 95%CI : -19.3, 7.85). Heterogeneity was significant between the studies (Q test P:<0.001, I^2 :97%(95%CI : 0-98.1%)), so a RE model was used.
- Ten studies (Figure 19) provided data for LOS. Meta-analysis of the data showed no statistically significant (p=0.33) difference between the two groups LOS (MWD:-0.74, 95%CI : -2.24, 0.76). Heterogeneity was significant between the studies (Q test P:<0.001, I^2 :91%(95%CI : 0-94.6%)), so a RE model was used.

Risk of bias across studies

Funnel plot of primary outcome (POPF) is shown in Figure 5. No study resides beyond the limits of 95% CI . Egger's test showed that there was no statistically significant publication bias (p=0.976).

DISCUSSION

Summary of evidence

Pancreaticoduodenectomy remains the most widely used surgical modality for the treatment of pancreatic head and periampullary tumors. Failure of the pancreatic anastomosis resulting in POPF has been identified as one of the most important factor of postoperative morbidity. It must also be mentioned that POPF is assumed to have a close relationship with other post PD complications, such as IAC, DGE and PPH [30 31]. As a result, surgeons, in an attempt to minimize post PD complications have meticulously compared the available anastomotic techniques.

In our study, after a systematic literature search, a meta-analysis of available RCTs was performed. In the qualitative and quantitative analysis, 10 studies with a total of 1629 patients were included. Regarding the primary outcome, PG was superior to PJ, thus, presenting lower rates of overall POPF. However this result was not confirmed when the two techniques were compared on the basis of clinically significant POPF, where no statistically significant difference was found. Heterogeneity in clinically significant POPF could possibly be the result of non uniformity in the definition of POPF. Although the included studies after 2005 were consistent with the 2005 ISGPS POPF definition, the remaining , defined POPF in an inconsistent way. DGE and clinically significant DGE were found to have no difference between PG and PJ, with a high level of heterogeneity though. As the operation type was not determined in most eligible studies, surgeons performed either PD or PPPD. The above mentioned heterogeneity could be explained in the light of lack of stratification regarding the operation type. Respectively, results from pooled data showed a lower rate of PPH for PJ, but no difference for clinically significant PPH. Heterogeneity for both of them was 0%, increasing thus the validity of these findings. The rate of biliary fistula and the intra abdominal fluid collection was not significantly different between PG and PJ, which diverges from the results of previous studies[32-35], due to inclusion of the recent RCTs [11 26]. Moreover, overall postoperative morbidity for both techniques was estimated at the level of 49%, complying with current literature [4]. Similarly, no difference was found in terms of mortality, reoperation rate, wound infection and perioperative blood transfusion. Finally, PG was not superior to PJ in terms of operation time and LOS. Heterogeneity was significantly high in these comparisons, possibly due to the approximate calculation of the mean and SD .

It is common knowledge between surgeons, that risk factors for development of POPF are the age, gender of the patient, preoperative jaundice and malnutrition, underlying pathology, pancreatic texture and pancreatic duct size, operative time, resection type, anastomotic technique, and intraoperative blood loss [36]. El Nakeeb et al.[31] , however, in a retrospective study of 471 patients, suggested that risk factors for POPF include the cirrhotic liver, BMI, soft pancreas, pancreatic diameter <3mm, and pancreatic duct near the posterior border. This is inconsistent with the results from our meta-analysis, were PG was proven superior to PJ for overall POPF, mainly due to the imbalance of the two groups (PG: 424, PJ:46) in the above mentioned study.

The superiority of PG over PJ in terms of POPF can be justified by some theoretical advantages. Firstly, due to the fact that the posterior wall of the stomach lies just above the pancreatic remnant, the tension between the stomach and the pancreatic stump is minimized. Secondly, the acidic gastric content prevent the activation of pancreatic enzymes and consequently the the anastomotic lysis. Moreover, compared to a jejunum loop, the stomach wall is thicker, thus stabilizing the anastomosis. Finally, the abundant stomach wall vascularization, decreases the chance of an anstomotic ischaemia. This may also be the reason of increased post PD PPH in the PG group, rendering perioperative meticulous haemostasis of utmost importance.

As far as postoperative endocrine and exocrine pancreatic function is concerned, data are scarce and inconsistent, thus making further analysis very difficult . Figueras et al. [25] reported a higher stool elastase level and significant lesser weight loss in the PG group. Comparing PG and IRPJ, El Nakeeb et al. [23], concluded that postoperative steatorrhea and need for pancreatic enzyme supplements was higher in the PG group, while post PD serum albumin was in a lower level in patients submitted to PG. In the most recent RCT, Keck et al. [11] found that the need for oral enzyme supplements in six months after surgery was lower in the PG group, with the rate of reported steatorrhea further decreasing after 12 months.

Our meta-analysis provides an up-to-date pooled , published only data, estimation of the rate of POPF and other postoperative complications between the two most popular anastomotic technique. Compared to other recent studies [12 37], it reports results not only in overall morbidity, but also in clinically significant complications, such as DGE and PPH.

Limitations

Several limitations should be taken into account before appraising the results of this meta-analysis. First of all, there is a diversity in the POPF definition among the included studies. It must be noted, though, that all studies after 2005 use the ISGPS definition. The included trials have also incorporotated, both PD and PPPD in their study groups and there was ,also, no stratification on the basis of the underlying pathology. Moreover, a lack of uniformity exists, regarding the surgical anastomotic technique that may possibly result in biased results. Factors, like the texture of pancreas and the pancreatic duct diameter might also influence the results. Another source of bias could be the perioperative use of glue and stents and the postoperative administration of somatostatin ,since not all studies reported these information. Finally, another factor that contributes in heterogeneity is the surgical experience in the applied anastomotic technique.

Conclusions

The present meta-analysis of RCTs, demonstrates that, PG has lower overall incidence of POPF and higher rate of PPH against PJ. There was no difference between the two anastomotic techniques regarding clinically significant POPF ,DGE, clinically significant DGE , clinically significant PPH , biliary fistula, intra-abdominal fluid collection, overall morbidity, mortality, reoperation rate, wound infection, intraoperative blood transfusion, operative time and LOS. Given several limitations, more large scale high quality RCTs are required for the effect of the anastomotic technique on the incidence of POPF to be clarified.

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APPENDIX

Tables

PMID	First author	Country	Publication year	RCT type	POPF definition
26135690	Keck	GERMANY	2016	multicenter ,randomized, controlled, observer- and patient-blinded trial	ISGPS (grade B/C)
25799130	Grendar	CANADA	2015	single-center randomized controlled trial	Radiologically proven anastomotic leak or

					continued drainage of lipase-rich fluid on PoD 10. Classification by ISGPS
24467711	El Nakeeb	EGYPT	2014	single center, prospective randomized study	ISGPS (grades A/B/C)
24264781	Figueras	SPAIN	2013	multicenter, prospective randomized study	ISGPS(grade B/C)
23643139	Topal	BELGIUM	2013	multicentre, randomised superiority trial	ISGPS(grade B/C)
22744638	Wellner	GERMANY	2012	single center, open, randomized controlled study	ISGPS(grade B/C)
19092337	Fernández-Cruz	SPAIN	2008	single center ,prospective randomized study	ISGPS(grade B/C)
16327486	Bassi	ITALY	2005	single center ,prospective and randomized study	Any clinical significant output of fluid, rich in amylase, confirmed by fistulography
15910726	Duffas	FRANCE	2005	multicenter, single blind, controlled randomized, trial	Fluid obtained through drains or percutaneous aspiration, containing at least 4 times normal serum values of amylase for 3 days or as anastomotic leaks shown by fistulography
7574936	Yeo	USA	1995	single center , prospective randomized trial	Drainage of greater than 50 mL of amylase rich fluid (greater than threefold elevation above upper limit of normal in serum) through the operatively placed drains on or after

Table 1. Included studies

First author	Sample size		Age		Gender (M/F)		Intervention	Comparator	Primary outcome	Follow up	Morbidity	
	PG	PJ	PG	PJ	PG	PJ					PG	PJ
Keck	171	149	68(35-86)	66(29-87)	95/76	93/56	PG	PJ	clinically relevant POPF,grade B or C	12 months	N/A	
Grendar	48	50	63.6 ± 13.1	68.1 ± 10.7	20/28	29/21	PG	PJ	rate of pancreatic anastomotic leak/fistula	N/A	29	24
El Nakeeb	45	45	58 (12–73)	54 (15–73)	23/22	27/18	PG	isolated Roux loop pancreaticojejunostomy	rate of POPF	12 months	17	14
Figueras	65	58	67 (35–80)	65.5 (42–80)	44/21	37/21	PG	PJ	rate of POPF	6 months	41	38
Topal	162	167	67.0 (60.6–73.5)	66.1 (59.4–74.6)	100/62	91/76	PG	PJ	clinically relevant POPF,grade B or C	2 months	100	99
Wellner	59	57	67 (34–	64 (23	27/32	29/28	PG	PJ	clinically relevant	90 days	N/A	

			84)	– 81)					POPF,grade B or C		
Fernández-Cruz	53	55	63 ± 13	63 ± 14	29/24	38/17	PG with gastric partition	PJ	rate of POPF	N/A	12	24
Bassi	69	82	59.3 (58.2–60.4)	55.5(54.5 – 56.6)	44/25	35/33	PG	PJ	rate of POPF	N/A	20	32
Duffas	81	68	58.2 ± 11	58.6 ± 12	51/30	35/33	PG	PJ	rate of one or more postoperative IACs	30 days	37	32
Yeo	73	72	61.5 ± 1.7	62.4 ± 1.4	33/40	38/34	PG	PJ	rate of POPF	N/A	36	31

Table 2. Study characteristics

First author	**Disease (PDAC/DD/AMP/DBD/OTHER**		**Operation type**	**pd/pppd**		**Technique**		**Operative time**		**Postoperative hospital stay**	
	PG	PJ		PG	PJ	PG	PJ	PG	PJ	PG	PJ
Keck	104/-/10/-/14	98/-/11/-/14	pd or pppd	37/134	28/121	dunking , pursestring or interrupted or combination suture	duct to mucosa or dunking, running or interrupted or combination suture	332(165–600)	337(165–565)	15(5–208)	16(3–129)
Grendar	N/A		pd or pppd	N/A		posterior gastrostomy,2 layers anastomosis	2-layer end-to-side anastomosis	349 ± 70	356 ± 65	17.4 ± 11.6	14.0 ± 5.4
El Nakeeb	26/2/17/0/0	20/4/19/2/0	pd	45/0	45/0	posterior gastrostomy,2 layers anastomosis	two layers end-to-side pancreaticojejunostomy	300 (210–420)	320 (240–480)	9 (4–34)	8 (5–41)
Figueras	33/6/8/8/10	29/10/7/3/19	pd or pppd	35/30	30/28	posterior gastrostomy double-layer invaginated	duct-to-mucosa pancreaticojejunostomy	330 (235–620)	305 (240–510)	12 (1–52)	15,5 (6–55)
Topal	98/11/23/28/2	107/14/28/15/3	pd or pppd	65/98	65/102	end-to-side telescoped antecolic posterior gastrostomy	end-to-side telescoped pancreaticojejunostomy	250 (210–320)	250 (210–310)	19 (14–25)	18 (14–25)
Wellner	26/3/9/2/8	30/2/7/2/10	pd or pppd	7/52	2/55	invagination, posterior pancreatogastrostomy with pursestring suture	duct-to mucosa pancreaticojejunostomy	404 (280–629)	443 (230–683)	15 (7–135)	17 (10–60)
Fernández-Cruz	26/1/12/8/9	28/1/10/7/9	pppd	0/53	0/55	End-to-side duct-to- mucosa pancreatogastrostomy	end-to-side duct mucosa anastomosis PPPD-PJ	300 ± 50	310 ± 60	12 ±2	16 ± 3
Bassi	32/1/13/1/22	28/1/11/2/40	pd or pppd	3/66	12/70	posterior single layer telescoped gastrostomy	single-layer pancreaticojejunal or duct to mucosa	337.2 (336.1–338.2)	359.3 (352.9–354.9)	14.2 (13.1–15.3)	15.4 (14.3–16.5)
Duffas	34/3/17/8/19	25/3/19/11/10	pd or pppd	63/18	50/18	depending surgeon's preference	depending surgeon's preference	6.5 ± 2.6 (h)	6.4 ± 2.2 (h)	20 (1–98)	21 (7–97)
Yeo	40/4/7	40/5/	pd or	13/	13/	posterior	end -to- end or	7.4 ±	7.2 ±	17.1 ±	17.7 ±

	/6/16	11/7/9	pppd	60	59	gastrostomy	end-to-side pancreaticojejunostomy	0.2(h)	0.2(h)	1.6	1.5

Table 3. Operative characteristics

First author	Stent		Postoperative octreotide		Anastomotic glue reinforcement		Drains		Pancreatic parenchyma (soft/hard)		Pancreatic duct diameter	
	PG	PJ	PG	PJ	PG	PJ	PG	PJ	PG	PJ	PG	PJ
Keck	N/A		N/A		N/A		N/A		95/66	83/62	94 (<3mm)	78
Grendar	10	39	42	39	N/A		38	44	25/23	18/32	3.8 ± 2.4 (mm)	4.3 ± 2.6
El Nakeeb	0	0	45	45	N/A		N/A		26/19	22/23	22 (<3mm)	21
Figueras	N/A		65	58	N/A		65	58	34/31	33/25	4 (1–15) (mm)	4 (1–11)
Topal	0	0	162	167	0	0	162	167	N/A		98 (<3mm)	102
Wellner	0	57	22	13	N/A		59	57	35/23	29/28	26 (<3mm)	18
Fernández-Cruz	53	55	0	0	N/A		53	55	24/29	25/30	3.0 ± 1.7 (mm)	3.0 ±1.6
Bassi	0	0	69	82	N/A		69	82	69/0	82/0	<5 mm	
Duffas	15	15	22	22	17	12	81	68	49/32	41/27	32 (<3mm)	31
Yeo	0	0	0	0	0	0	73	72	16/21	17/28	3.4 ± 0.2 (mm)	2.9 ± 0.2

Table 4. Intraoperative characteristics

Figures

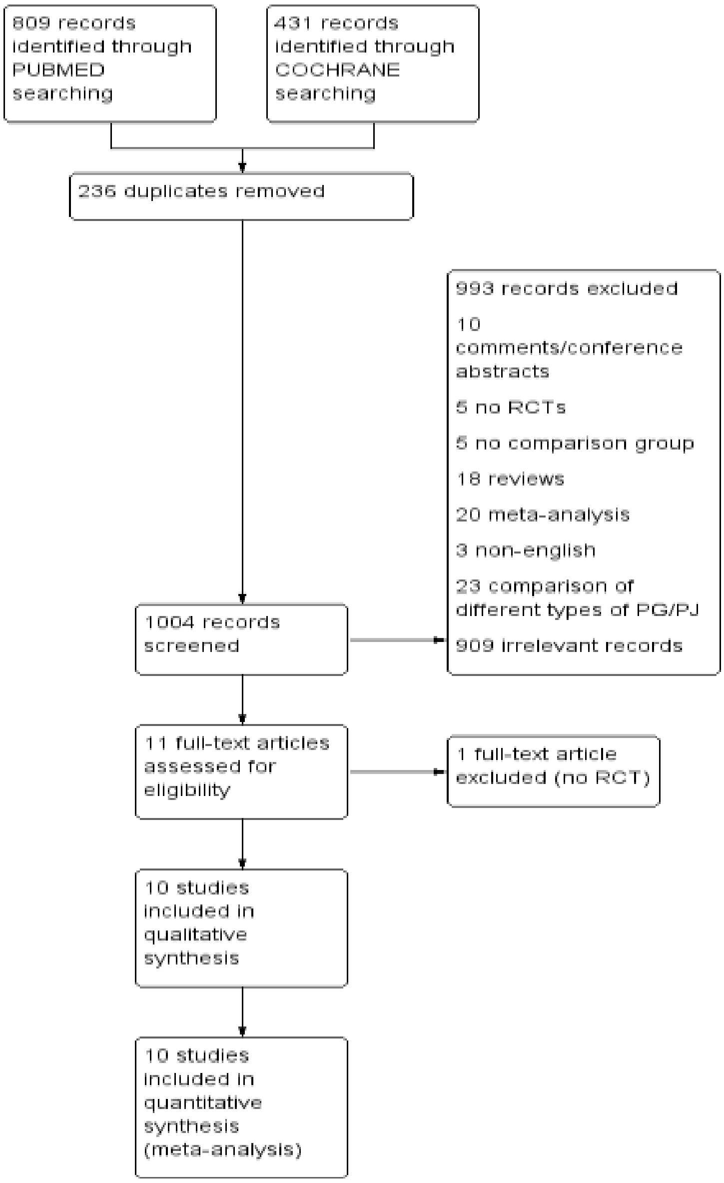

Figure 1. Study flow diagram

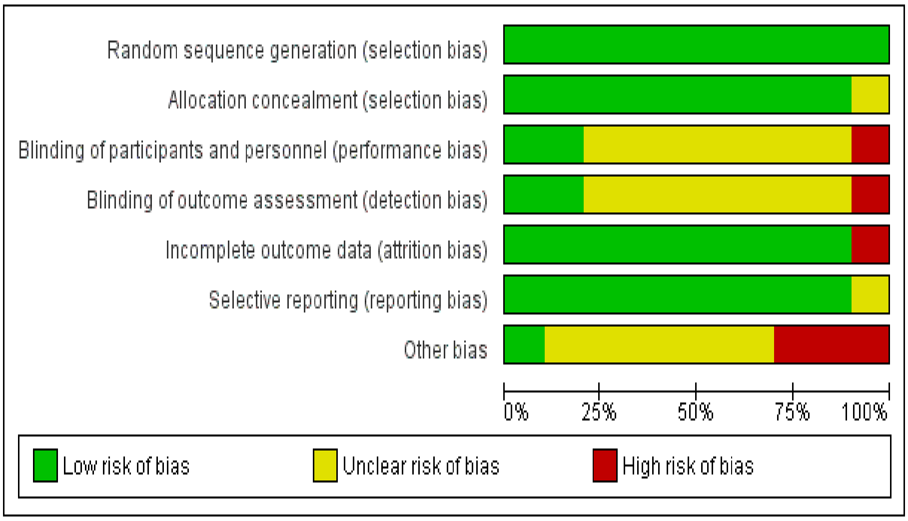

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

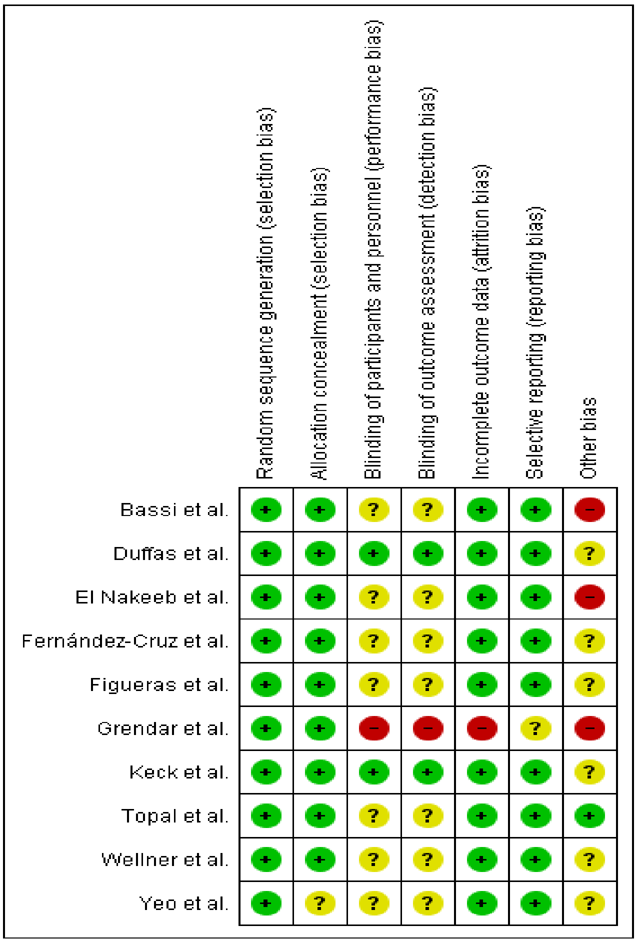

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bassi et al.	9	69	13	82	7.0%	0.80 [0.32, 1.99]
Duffas et al.	13	81	14	68	8.7%	0.74 [0.32, 1.70]
El Nakeeb et al.	10	45	9	45	4.8%	1.14 [0.41, 3.15]
Fernández-Cruz et al.	2	53	10	55	6.4%	0.18 [0.04, 0.85]
Figueras et al.	10	65	20	58	12.2%	0.35 [0.15, 0.82]
Grendar et al.	12	48	9	50	4.5%	1.52 [0.57, 4.02]
Keck et al.	34	171	33	149	19.3%	0.87 [0.51, 1.50]
Topal et al.	33	162	52	167	27.8%	0.57 [0.34, 0.94]
Wellner et al.	6	59	7	57	4.4%	0.81 [0.25, 2.57]
Yeo et al.	9	73	8	72	4.8%	1.13 [0.41, 3.10]
Total (95% CI)		**826**		**803**	**100.0%**	**0.71 [0.55, 0.91]**
Total events	138		175			

Heterogeneity: Chi² = 11.12, df = 9 (P = 0.27); I² = 19%
Test for overall effect: Z = 2.66 (P = 0.008)

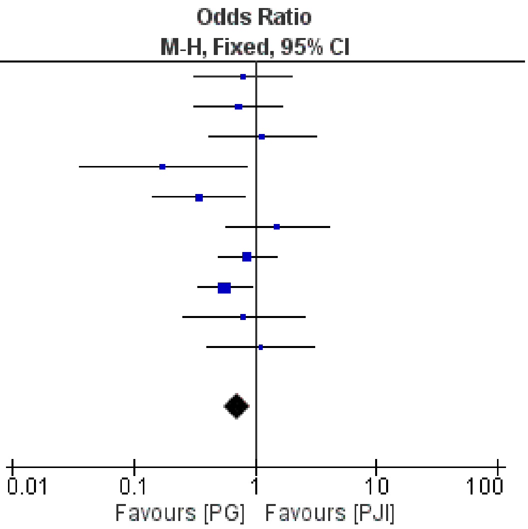

Figure 4. Postoperative pancreatic fistula

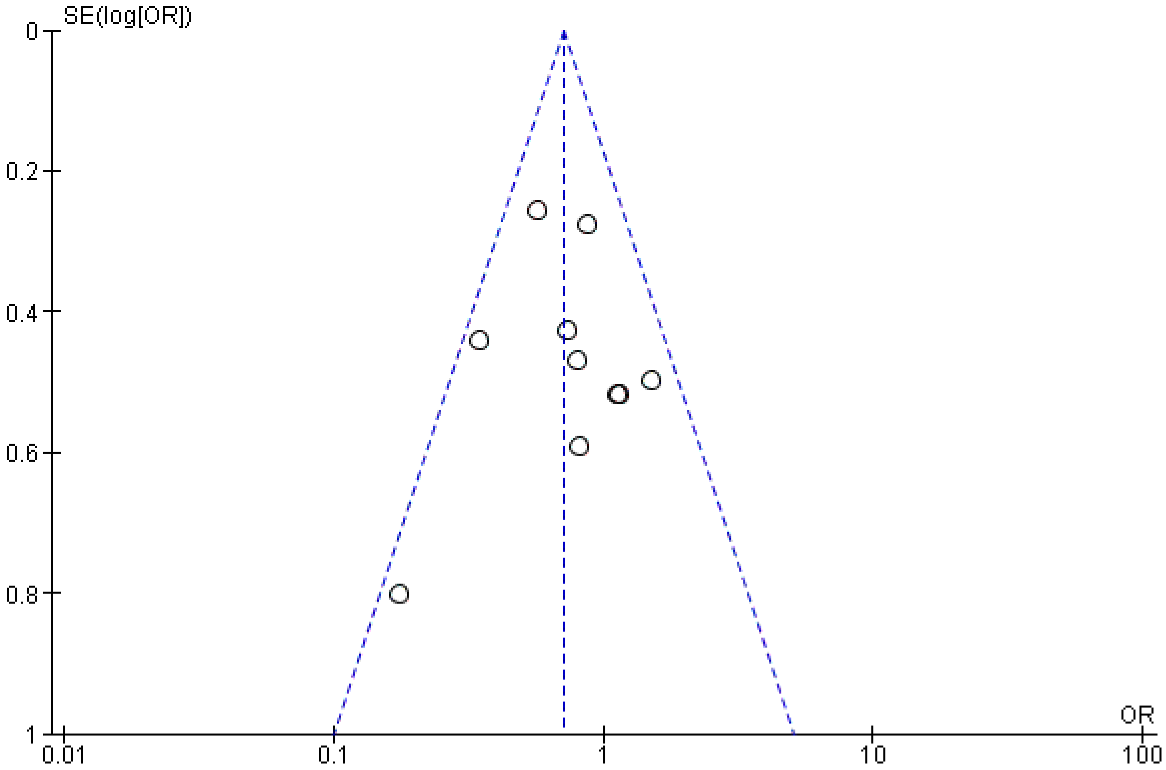

Figure 5. Funnel plot of comparison: Postoperative pancreatic fistula.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Random, 95% CI
Bassi et al.	9	69	13	82	10.6%	0.80 [0.32, 1.99]
Duffas et al.	13	81	11	68	11.1%	0.99 [0.41, 2.38]
El Nakeeb et al.	7	45	4	45	6.9%	1.89 [0.51, 6.97]
Fernández-Cruz et al.	2	53	10	55	5.3%	0.18 [0.04, 0.85]
Figueras et al.	7	65	19	58	10.2%	0.25 [0.10, 0.65]
Grendar et al.	8	48	6	50	8.3%	1.47 [0.47, 4.59]
Keck et al.	34	171	33	149	16.1%	0.87 [0.51, 1.50]
Topal et al.	13	162	33	167	13.8%	0.35 [0.18, 0.70]
Wellner et al.	6	59	7	57	8.1%	0.81 [0.25, 2.57]
Yeo et al.	9	73	8	72	9.5%	1.13 [0.41, 3.10]
Total (95% CI)		**826**		**803**	**100.0%**	**0.70 [0.46, 1.06]**
Total events	108		144			

Heterogeneity: Tau² = 0.20; Chi² = 17.40, df = 9 (P = 0.04); I² = 48%
Test for overall effect: Z = 1.68 (P = 0.09)

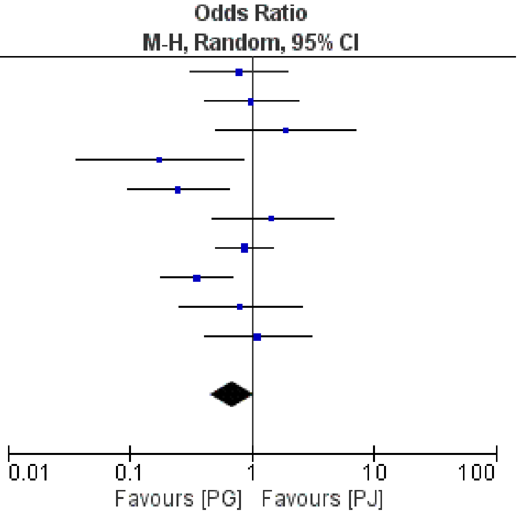

Figure 6. Clinically significant postoperative pancreatic fistula

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Random, 95% CI
Bassi et al.	2	69	10	82	6.5%	0.21 [0.05, 1.02]
El Nakeeb et al.	9	45	4	45	8.7%	2.56 [0.73, 9.03]
Fernández-Cruz et al.	2	53	8	55	6.2%	0.23 [0.05, 1.14]
Figueras et al.	19	65	15	58	14.6%	1.18 [0.54, 2.62]
Keck et al.	64	171	60	149	20.8%	0.89 [0.57, 1.39]
Topal et al.	25	162	13	167	16.0%	2.16 [1.06, 4.39]
Wellner et al.	14	59	9	57	12.5%	1.66 [0.65, 4.21]
Yeo et al.	16	73	16	72	14.7%	0.98 [0.45, 2.15]
Total (95% CI)		**697**		**685**	**100.0%**	**1.08 [0.68, 1.70]**
Total events	151		135			

Heterogeneity: Tau² = 0.21; Chi² = 14.90, df = 7 (P = 0.04); I² = 53%
Test for overall effect: Z = 0.32 (P = 0.75)

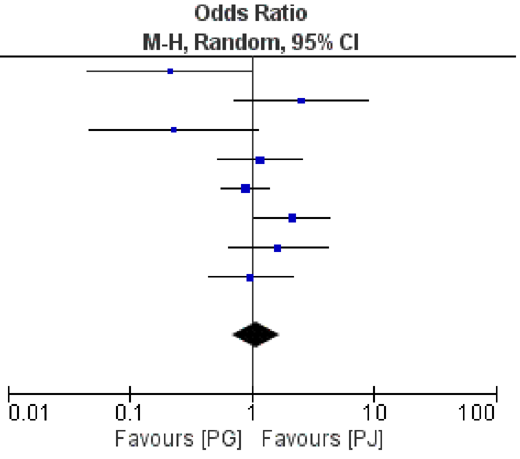

Figure 7. Delayed gastric emptying.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Random, 95% CI
Bassi et al.	2	69	10	82	7.5%	0.21 [0.05, 1.02]
El Nakeeb et al.	9	45	4	45	9.8%	2.56 [0.73, 9.03]
Fernández-Cruz et al.	2	53	8	55	7.2%	0.23 [0.05, 1.14]
Figueras et al.	9	65	11	58	13.0%	0.69 [0.26, 1.80]
Keck et al.	20	171	21	149	17.3%	0.81 [0.42, 1.56]
Topal et al.	25	162	13	167	16.5%	2.16 [1.06, 4.39]
Wellner et al.	14	59	9	57	13.4%	1.66 [0.65, 4.21]
Yeo et al.	16	73	16	72	15.4%	0.98 [0.45, 2.15]
Total (95% CI)		**697**		**685**	**100.0%**	**0.98 [0.59, 1.63]**
Total events	97		92			

Heterogeneity: Tau² = 0.28; Chi² = 15.73, df = 7 (P = 0.03); I² = 55%
Test for overall effect: Z = 0.08 (P = 0.93)

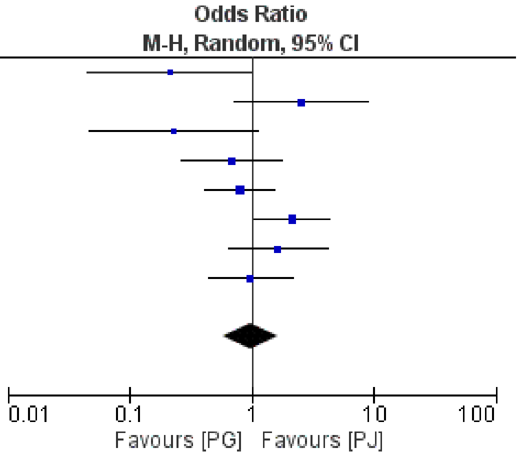

Figure 8. Clinically significant delayed gastric emptying.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bassi et al.	3	69	6	82	9.6%	0.58 [0.14, 2.39]
Duffas et al.	13	81	9	68	15.0%	1.25 [0.50, 3.14]
El Nakeeb et al.	4	45	2	45	3.3%	2.10 [0.36, 12.08]
Fernández-Cruz et al.	1	53	1	55	1.8%	1.04 [0.06, 17.04]
Figueras et al.	13	65	7	58	10.8%	1.82 [0.67, 4.93]
Keck et al.	36	171	17	149	26.2%	2.07 [1.11, 3.87]
Topal et al.	21	162	17	167	26.6%	1.31 [0.67, 2.59]
Wellner et al.	6	59	4	57	6.7%	1.50 [0.40, 5.62]
Total (95% CI)		**705**		**681**	**100.0%**	**1.52 [1.08, 2.14]**
Total events	97		63			

Heterogeneity: Chi² = 3.40, df = 7 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

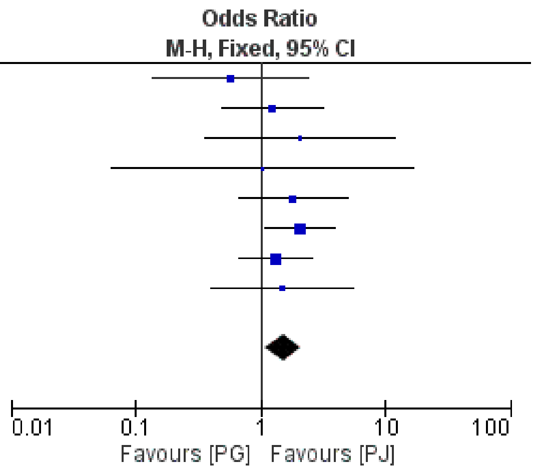

Figure 9. Postpancreatectomy haemorrhage.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bassi et al.	3	69	6	82	10.0%	0.58 [0.14, 2.39]
Duffas et al.	13	81	9	68	15.7%	1.25 [0.50, 3.14]
El Nakeeb et al.	4	45	2	45	3.5%	2.10 [0.36, 12.08]
Fernández-Cruz et al.	1	53	1	55	1.8%	1.04 [0.06, 17.04]
Figueras et al.	11	65	7	58	11.7%	1.48 [0.53, 4.12]
Keck et al.	27	171	16	149	27.5%	1.56 [0.80, 3.02]
Topal et al.	21	162	17	167	27.8%	1.31 [0.67, 2.59]
Wellner et al.	2	59	1	57	1.9%	1.96 [0.17, 22.29]
Total (95% CI)		**705**		**681**	**100.0%**	**1.35 [0.95, 1.93]**
Total events	82		59			

Heterogeneity: Chi² = 1.99, df = 7 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)

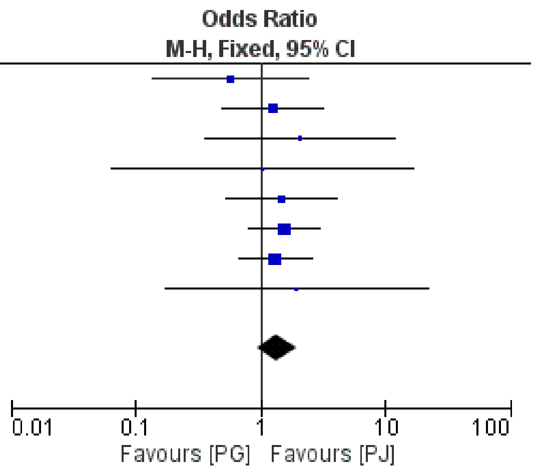

Figure 10. Clinically significant postpancreatectomy haemorrhage.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bassi et al.	0	69	7	82	24.1%	0.07 [0.00, 1.29]
Duffas et al.	6	81	2	68	7.1%	2.64 [0.52, 13.53]
El Nakeeb et al.	6	45	4	45	12.3%	1.58 [0.41, 6.02]
Fernández-Cruz et al.	0	53	1	55	5.2%	0.34 [0.01, 8.52]
Figueras et al.	1	65	6	58	22.1%	0.14 [0.02, 1.16]
Keck et al.	3	171	5	149	18.6%	0.51 [0.12, 2.19]
Yeo et al.	1	73	3	72	10.6%	0.32 [0.03, 3.15]
Total (95% CI)		**557**		**529**	**100.0%**	**0.58 [0.31, 1.06]**
Total events	17		28			

Heterogeneity: Chi² = 9.62, df = 6 (P = 0.14); I² = 38%
Test for overall effect: Z = 1.78 (P = 0.08)

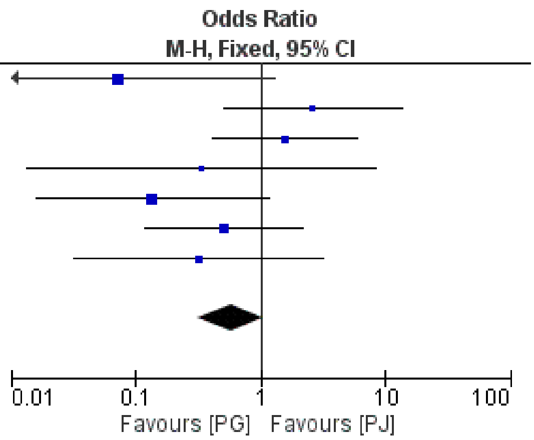

Figure 11. Biliary fistula.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Random, 95% CI
Bassi et al.	7	69	22	82	13.1%	0.31 [0.12, 0.77]
Duffas et al.	11	81	16	68	14.2%	0.51 [0.22, 1.19]
El Nakeeb et al.	6	45	4	45	8.3%	1.58 [0.41, 6.02]
Fernández-Cruz et al.	2	53	8	55	6.4%	0.23 [0.05, 1.14]
Figueras et al.	5	65	10	58	10.3%	0.40 [0.13, 1.25]
Keck et al.	33	171	31	149	19.5%	0.91 [0.53, 1.58]
Topal et al.	9	162	21	167	14.7%	0.41 [0.18, 0.92]
Wellner et al.	7	59	3	57	7.8%	2.42 [0.59, 9.88]
Yeo et al.	4	73	2	72	5.7%	2.03 [0.36, 11.44]
Total (95% CI)		**778**		**753**	**100.0%**	**0.64 [0.40, 1.02]**
Total events	84		117			

Heterogeneity: Tau² = 0.21; Chi² = 14.57, df = 8 (P = 0.07); I² = 45%
Test for overall effect: Z = 1.86 (P = 0.06)

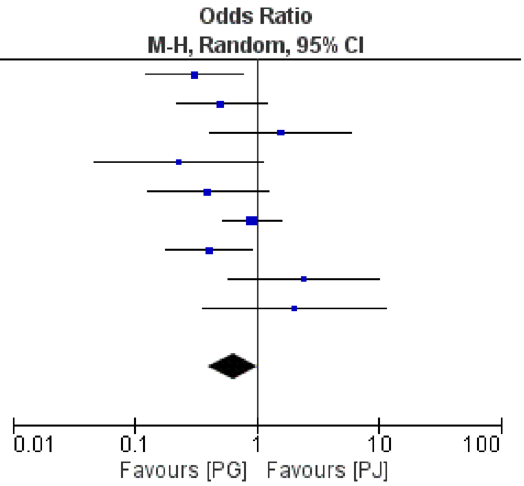

Figure 12. Intra-abdominal fluid collection.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bassi et al.	20	69	32	82	14.4%	0.64 [0.32, 1.26]
Duffas et al.	37	81	32	68	13.1%	0.95 [0.50, 1.81]
El Nakeeb et al.	17	45	14	45	6.1%	1.34 [0.56, 3.22]
Fernández-Cruz et al.	12	53	24	55	12.7%	0.38 [0.16, 0.87]
Figueras et al.	41	65	38	58	10.3%	0.90 [0.43, 1.88]
Grendar et al.	29	48	24	50	6.5%	1.65 [0.74, 3.69]
Topal et al.	100	162	99	167	25.9%	1.11 [0.71, 1.72]
Yeo et al.	36	73	31	72	11.0%	1.29 [0.67, 2.48]
Total (95% CI)		**596**		**597**	**100.0%**	**0.97 [0.77, 1.23]**
Total events	292		294			

Heterogeneity: Chi² = 9.68, df = 7 (P = 0.21); I² = 28%
Test for overall effect: Z = 0.22 (P = 0.82)

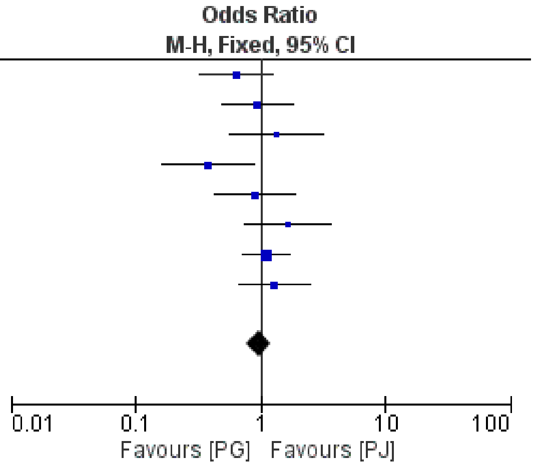

Figure 13. Morbidity.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bassi et al.	0	69	1	82	4.3%	0.39 [0.02, 9.75]
Duffas et al.	10	81	7	68	21.2%	1.23 [0.44, 3.42]
El Nakeeb et al.	4	45	3	45	8.7%	1.37 [0.29, 6.48]
Fernández-Cruz et al.	0	53	0	55		Not estimable
Figueras et al.	3	65	3	58	9.6%	0.89 [0.17, 4.58]
Grendar et al.	2	48	1	50	3.0%	2.13 [0.19, 24.30]
Keck et al.	10	169	8	148	25.5%	1.10 [0.42, 2.87]
Topal et al.	4	162	8	167	24.4%	0.50 [0.15, 1.70]
Wellner et al.	1	59	1	57	3.2%	0.97 [0.06, 15.81]
Yeo et al.	0	73	0	72		Not estimable
Total (95% CI)		**824**		**802**	**100.0%**	**0.98 [0.60, 1.61]**
Total events	34		32			

Heterogeneity: Chi² = 2.28, df = 7 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)

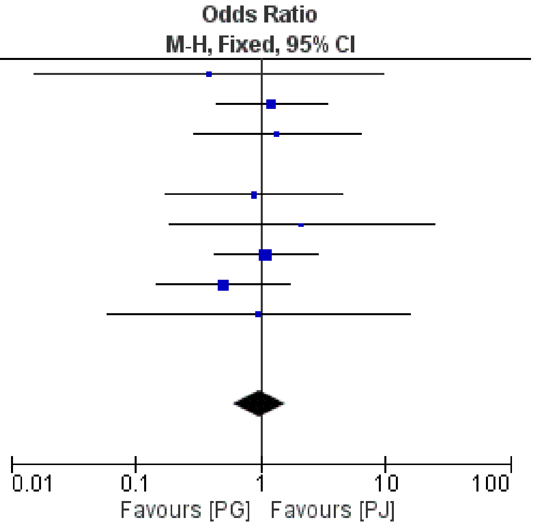

Figure 14. Mortality.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bassi et al.	5	69	5	82	6.5%	1.20 [0.33, 4.34]
Duffas et al.	15	81	15	68	20.3%	0.80 [0.36, 1.79]
El Nakeeb et al.	4	45	3	45	4.2%	1.37 [0.29, 6.48]
Fernández-Cruz et al.	1	53	1	55	1.5%	1.04 [0.06, 17.04]
Keck et al.	20	171	27	149	38.9%	0.60 [0.32, 1.12]
Topal et al.	14	162	17	167	23.3%	0.83 [0.40, 1.75]
Wellner et al.	7	59	4	57	5.5%	1.78 [0.49, 6.46]
Yeo et al.	0	73	0	72		Not estimable
Total (95% CI)		**713**		**695**	**100.0%**	**0.84 [0.59, 1.20]**
Total events	66		72			

Heterogeneity: Chi² = 3.15, df = 6 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

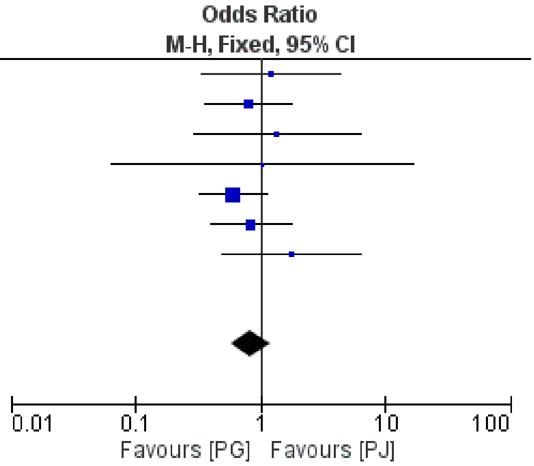

Figure 15. Reoperation.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
El Nakeeb et al.	2	45	3	45	9.4%	0.65 [0.10, 4.10]
Fernández-Cruz et al.	3	53	2	55	6.0%	1.59 [0.25, 9.92]
Keck et al.	20	171	18	149	55.4%	0.96 [0.49, 1.90]
Yeo et al.	14	73	11	72	29.2%	1.32 [0.55, 3.13]
Total (95% CI)		**342**		**321**	**100.0%**	**1.08 [0.66, 1.76]**
Total events	39		34			

Heterogeneity: Chi² = 0.77, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)

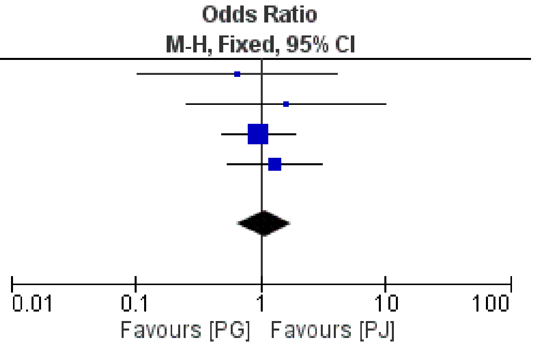

Figure 16. Wound Infection.

Study or Subgroup	PG Events	PG Total	PJ Events	PJ Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bassi et al.	5	69	5	82	7.0%	1.20 [0.33, 4.34]
Duffas et al.	19	81	12	68	16.6%	1.43 [0.64, 3.21]
Fernández-Cruz et al.	15	53	16	55	18.7%	0.96 [0.42, 2.22]
Grendar et al.	5	48	13	50	19.0%	0.33 [0.11, 1.02]
Keck et al.	25	171	17	149	25.8%	1.33 [0.69, 2.57]
Wellner et al.	9	59	9	57	12.9%	0.96 [0.35, 2.62]
Total (95% CI)		**481**		**461**	**100.0%**	**1.03 [0.72, 1.47]**
Total events	78		72			

Heterogeneity: Chi² = 5.25, df = 5 (P = 0.39); I² = 5%
Test for overall effect: Z = 0.17 (P = 0.86)

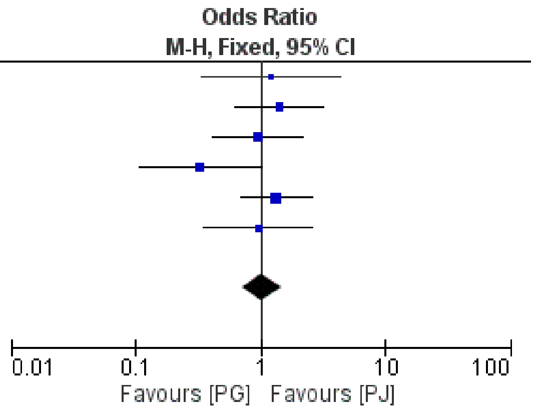

Figure 17. Blood transfusion.

Study or Subgroup	PG Mean	PG SD	PG Total	PJ Mean	PJ SD	PJ Total	Weight	Mean Difference IV, Random, 95% CI
Bassi et al.	337.2	4.23	69	359.3	4.61	82	13.3%	-22.10 [-23.51, -20.69]
Duffas et al.	390	156	81	384	132	68	5.2%	6.00 [-40.24, 52.24]
El Nakeeb et al.	300	52.5	45	320	60	45	9.6%	-20.00 [-43.29, 3.29]
Fernández-Cruz et al.	300	50	53	310	60	55	10.2%	-10.00 [-30.80, 10.80]
Figueras et al.	330	96.25	65	305	67.5	58	8.3%	25.00 [-4.14, 54.14]
Grendar et al.	349	70	48	356	65	50	8.8%	-7.00 [-33.77, 19.77]
Keck et al.	332	72.5	171	337	66.6	149	11.4%	-5.00 [-20.25, 10.25]
Topal et al.	250	18.3	162	250	16.6	167	13.2%	0.00 [-3.78, 3.78]
Wellner et al.	404	87.25	59	443	113.25	57	6.7%	-39.00 [-75.88, -2.12]
Yeo et al.	444	12	73	432	12	72	13.2%	12.00 [8.09, 15.91]
Total (95% CI)			**826**			**803**	**100.0%**	**-5.73 [-19.30, 7.85]**

Heterogeneity: Tau² = 359.13; Chi² = 350.82, df = 9 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.83 (P = 0.41)

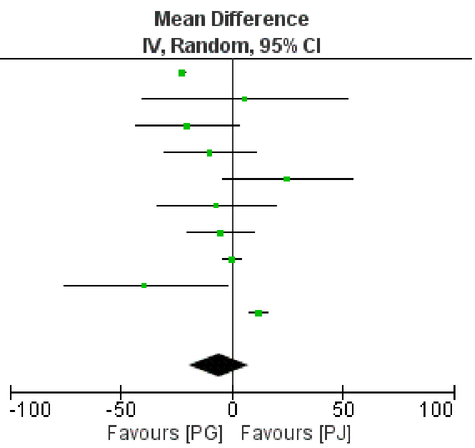

Figure 18. Operative time.

Study or Subgroup	PG Mean	PG SD	PG Total	PJ Mean	PJ SD	PJ Total	Weight	Mean Difference IV, Random, 95% CI
Bassi et al.	14.2	4.65	69	15.4	5.07	82	14.5%	-1.20 [-2.75, 0.35]
Duffas et al.	20	16.16	81	21	22.5	68	4.2%	-1.00 [-7.40, 5.40]
El Nakeeb et al.	9	7.5	45	8	9	45	9.1%	1.00 [-2.42, 4.42]
Fernández-Cruz et al.	12	2	53	16	3	55	16.0%	-4.00 [-4.96, -3.04]
Figueras et al.	12	12.75	65	15.5	12.25	58	6.9%	-3.50 [-7.92, 0.92]
Grendar et al.	17.4	11.6	48	14	5.4	50	8.6%	3.40 [-0.21, 7.01]
Keck et al.	15	33.8	171	16	21	149	4.5%	-1.00 [-7.09, 5.09]
Topal et al.	19	1.83	162	18	1.83	167	16.9%	1.00 [0.60, 1.40]
Wellner et al.	15	32	59	17	12.5	57	2.5%	-2.00 [-10.79, 6.79]
Yeo et al.	17.1	1.6	73	17.7	1.5	72	16.8%	-0.60 [-1.10, -0.10]
Total (95% CI)			**826**			**803**	**100.0%**	**-0.74 [-2.24, 0.76]**

Heterogeneity: $Tau^2 = 3.43$; $Chi^2 = 105.57$, $df = 9$ ($P < 0.00001$); $I^2 = 91\%$
Test for overall effect: $Z = 0.97$ ($P = 0.33$)

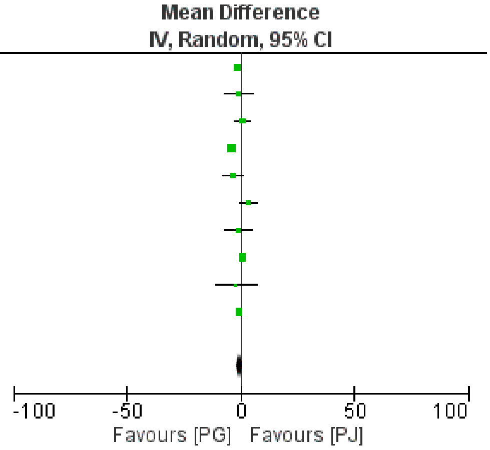

Figure 19. Length of hospital stay.